

REMARKS

Claims 1, 2, 14, 17-20, 23, 29, and 32-55 are pending in this application. Claims 1, 2, 14, 17-20, 23, 29, 32-40, and 42-55 are rejected under 35 U.S.C. § 112, first paragraph. All of the claims are further rejected under 35 U.S.C. § 102(b) for lack of novelty and under 35 U.S.C. § 103(a) for obviousness. All of the claims also stand rejected under the judicially created doctrine of obviousness-type double patenting. Each of the Office's rejections is addressed below. Applicants respectfully request reconsideration of the claims as amended.

Support for the amendments

Claims 2, 14, 20, 32, 33, 39-43, 45-46, and 48-53 have been cancelled. Applicants reserve the right to pursue all cancelled subject matter in this or a continuing application. Claims 1, 19, 37-38, 44, 47, and 55 have been amended to recite the limitation that the humanized monoclonal antibody specifically binds the Shiga toxin protein. Support for this limitation is found throughout the specification, for example, at page 4, lines 19-21; page 7, line 18 and line 21; page 18, lines 17-18; and page 27, lines 4-5. Independent claim 1 and dependent claims 37, 38, and 44 have been amended to recite the limitation that the antibody includes the variable region sequences provided in SEQ ID NOs: 19, 21, 42, or 44. Independent claim 19 and dependent claim 47 have been amended to recite the limitation that the antibody includes the murine 11E10 antibody (ATCC Accession No.

CRL 1987) variable region. Support for these amendments may be found, for example, in previous claims 19, 37, 38, 43, and in the specification, for example, at page 11, lines 4-10 and page 19, lines 12-18. New independent claim 56 and dependent claims 57-63 are directed to a humanized monoclonal antibody that specifically binds to Stx1 and Stx1 variants and includes the murine 13C4 antibody (ATCC Accession NO. CRL 1794) variable region. Dependent claims 57-63 recite human constant regions and combined compositions that further include a humanized monoclonal antibody that specifically binds to Stx2 and includes the murine 11E10 antibody (ATCC Accession NO. CRL 1987) variable region. Support for these claims may be found, for example, in previous claims 17-18 and throughout the specification, for example, at page 11, lines 4-10; page 19, lines 12-18; and page 32, lines 11 to 15. No new matter has been added by these amendments.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1, 2, 14, 17-20, 23, 29, 32-40, and 42-55 are variously rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description and enablement rejections. Each of the rejections is addressed below.

Enablement

Claims 1, 2, 14, 17-20, 23, 29, 32-40, and 43-44 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. In making the

enablement rejection, the Examiner acknowledges that Applicants' specification enables humanized monoclonal antibodies based on monoclonal antibodies 13C4 or 11E10, but maintains the rejection on the grounds that the specification does not enable a genus of human antibodies that specifically reacts with the Stx1 or Stx2 antigen wherein the antibodies contain at least a part of a given murine immunoglobulin variable region. The Examiner further states that the specification does not provide enablement for pharmaceutical compositions that comprise humanized antibodies containing at least a part of a given murine immunoglobulin variable region. As applied to the current claims, this rejection may be withdrawn.

While not agreeing with the Examiner, in order to expedite prosecution, Applicants have amended the claims to recite only the antibody species that the Examiner has indicated as allowable. Specifically, claims 1, 37, 38, and 44 have been amended to recite the limitation that the antibody comprises the immunoglobulin heavy chain and light chain variable regions shown in Figure 3 (SEQ ID NOs: 19 and 21) or the immunoglobulin heavy chain and light chain variable regions shown in Figure 6 (SEQ ID NOs: 42 and 44). Claims 19 and 47 and new claims 56 and 61 recite the limitation that the antibody comprises either the murine 11E10 (ATCC accession no. CRL 1987) or the murine 13C4 (ATCC CRL 1794) variable region. All remaining claims depend from one of these claims and, by definition, include the limitations to the defined variable regions. As indicated by the Examiner at pages 4, 6, 7, and 8 of the Office Action, the

specification is enabling for “humanized monoclonal antibodies based on monoclonal antibodies 13C4 or 11E10 (defined regions)” (Office Action, page 4). With regard to the asserted lack of enablement for the pharmaceutical compositions, the Examiner also states that the specification is enabling for “pharmaceutical compositions comprising humanized monoclonal antibodies based on monoclonal antibodies 13C4 or 11E10 (defined sequences)” (Office Action, page 7-8). In view of the Examiner’s indication that this subject matter is allowable, Applicants submit that the enablement rejection can now be withdrawn.

Written Description

In setting forth the written description rejection of claims 1, 2, 14, 17-20, 23, 29, 32-40, and 42-55, the Examiner states that, “a genus of humanized antibodies, the members of which specifically reacts with the Stx1 or Stx 2 antigen wherein said antibodies contain at least part of a given immunoglobulin variable region” are not sufficiently described in the specification in such a way to reasonably convey to one skilled in the art that the inventor, at the time the application was filed, had possession of the claimed invention.

At page 13 the Examiner states that, “only the specific antibodies disclosed in the specification that are produced from murine antibodies 13C4 and 11E10 meet the written description requirement.” While not agreeing with the Examiner, in order to expedite

prosecution, Applicants have amended the claims to recite only the antibody species that the Examiner has indicated would be allowable. The presently amended claims recite the limitation that the antibody includes the variable regions of 13C4 or 11E10 as indicated either by SEQ ID NOs: 19, 21, 42, or 44 or by the ATCC deposit number for the murine 13C4 and 11E10 antibodies. The rejection of claims 1, 2, 14, 17-20, 23, 29, 32-40, and 42-55 for failing to comply with the written description requirement can be withdrawn.

Rejection under 35 U.S.C. § 102(b)

Claims 1, 2, 14, 17-20, 23, 29, and 32-55 were rejected under 35 U.S.C. § 102(b) as being anticipated by Edwards et al. (V110/11:113 page 113 (1997)). In view of the Declaration of Dr. Hing Wong submitted herewith, Applicants respectfully request that this rejection be withdrawn.

Applicants note that, in making the rejection, the Examiner states that the rejection is under § 102(b) but recites the statute under § 102(a). For clarification, Applicants provide herewith, as Exhibit A, a copy of the publication from the 3rd International Symposium and Workshop on Shiga Toxin (Verocytotoxin)-Producing Escherichia Coli Infections in which this abstract was published. As indicated on the cover of the publication, the workshop took place on June 22-26, 1997. The priority date for the present application is December 23, 1997 (the filing date for U.S. provisional application number 60/068,635), a priority date to which the currently claimed subject matter is

entitled. Accordingly, Edwards et al. was published less than a year before the priority date of the present application and should be considered only under § 102(a).

As set forth under M.P.E.P. § 2132.01, a rejection under 35 U.S.C. § 102(a) over a publication whose authorship differs in any way from the inventive entity can be overcome by submission of a specific declaration by the Applicants establishing that the article is describing Applicants' own work. Here, Applicants direct the Examiner's attention to the enclosed Declaration by inventor Dr. Hing Wong. In this Declaration, Dr. Wong states (paragraph 2):

The experiments described in the Edwards et al. ((V110/11:113 page 113 (1997)) publication that relate to the invention were the joint contribution of the instant inventors alone, notwithstanding the inclusion of additional authors on the publication. The other named authors, Ana Edwards and Kathy Arbuthnott, acted on matters concerning the invention under the direction and supervision of the named inventors, and did not contribute to the conception of the presently claimed invention.

The Wong Declaration clearly establishes that the authors of the Edwards publication who are not the instant inventors did not contribute to the conception of the presently claimed invention, and that any experiments described in the Edwards publication that relate to the claimed invention are Applicants' own work. The § 102(a) rejection over Edwards should be withdrawn.

Rejections under 35 U.S.C. §103(a)

Claims 1, 2, 14, 17-20, 23, 29, and 32-55 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Speirs et al. (*Canadian Journal of Microbiology*, 37:650-653, 1991; “Speirs”) or O’Brien et al. (U.S. Patent No. 5,747,272; “O’Brien”) in view of Carter et al. (WO 94/04679; “Carter”) or Shitara et al. (U.S. Patent No. 5,866,692; “Shitara”) and further in view of Tzipori et al. (U.S. Patent Application Publication No. 2003/0082189; “Tzipori”). Speirs and O’Brien are cited for disclosing the mouse 13C4 and 11E10 antibodies. Carter and Shitara are relied upon for disclosing methods of producing humanized antibodies. Tzipori is cited for disclosing that monoclonal antibodies specific for Shiga toxins can be used to treat hemolytic uremic syndrome. Applicants respectfully traverse this rejection.

Applicants’ invention features humanized monoclonal antibodies that specifically bind to Stx1 or Stx2 protein. As presently amended, all of the claimed antibodies feature a human immunoglobulin constant region and a defined murine variable region. The defined murine variable regions are indicated by either the SEQ ID NOs or by the ATCC deposit number of the anti-Stx1 or anti-Stx2 murine antibody. For example, claim 1, as amended, recites the limitation that the humanized monoclonal antibody includes the variable region sequences of SEQ ID NOs: 19 and 21 (for binding to Stx1) or the variable region sequences of SEQ ID NOs: 42 and 44 (for binding to Stx2). Claim 19, as amended, recites the limitation that the humanized monoclonal antibody that binds to

Stx2 includes the murine 11E10 (ATCC Accession No. CRL 1987) variable region.

Claim 47, as amended, recites the limitation that the humanized monoclonal antibody that binds to Stx1 includes the murine 13C4 (ATCC Accession No. CRL 1794) variable region. Applicants submit that there is nothing in the references of record that provides a basis for selecting either 13C4 or 11E10 as a candidate antibody for humanization to arrive at the *defined antibodies as presently claimed*.

Speirs and O'Brien describe using the mouse 13C4 and 11E10 antibodies in a diagnostic kit for detecting Shiga-like toxins. There is nothing in Speirs or O'Brien that teaches, suggests, or motivates the skilled worker to use their antibodies in a therapeutic application to treat a Shiga toxin induced disease, much less a teaching to humanize these antibodies for that purpose. The ability of an antibody to detect a Shiga-like toxin in an *in vitro diagnostic assay* does not necessarily translate into an ability to effectively neutralize a Shiga-like toxin or protect an animal against a challenge with a Shiga toxin *in vivo* as shown for the claimed antibodies in Examples 7 and 8 of the present specification.

Carter and Shitara describe general methods for humanizing an antibody, and each fails to describe or even mention either the 13C4 or 11E10 antibody.

The Examiner states that Tzipori provided the necessary motivation to humanize the antibodies "in order to use them in the treatment methodologies disclosed." Tzipori, however, fails to provide motivation to produce the claimed humanized 13C4 and 11E10 antibodies because Tzipori describes completely different antibodies and fails to even

mention 13C4 or 11E10. Tzipori's teachings include methods for the treatment of hemolytic uremic syndrome using antibodies to Shiga like toxins (SLT-I and SLT-II) that are completely unrelated to the presently claimed antibodies. Tzipori describes the generation of mouse monoclonal antibodies against Shiga-like toxins and provides one *in vivo* assay that includes the treatment of piglets with immune serum from piglets previously immunized with a Shiga like toxin. This therapeutic regimen did not include the use of mouse antibodies to Shiga like toxins, let alone the 13C4 or 11E10 antibodies, humanized or otherwise.

Moreover, Applicants point out that at the time Tzipori's priority application was filed, the 13C4 and 11E10 mouse monoclonal antibodies had been known in the art as diagnostic reagents for *over five years* (Speirs was published in August of 1991 and Tzipori's priority application was filed on November 15, 1996). Tzipori, however, chose to use completely different antibodies for the treatment of hemolytic uremic syndrome. The fact that Tzipori choose not to use the 13C4 and 11E10 antibodies or to humanize the 13C4 and 11E10 antibodies, although they were known in the art, underscores the nonobviousness of the humanized 13C4 and 11E10 antibodies as presently claimed. Applicants submit that a skilled artisan, upon reading Tzipori, would not be motivated to choose an antibody that Tzipori himself chose not to use, and to humanize that antibody in order to arrive at the presently claimed humanized antibodies or combination of antibodies.

Absent a motivation to combine references, the Examiner has not shown a proper *prima facie* case of obviousness, and the rejection of the claims under § 103 for obviousness over Speirs or O'Brien in view of Carter or Shitara and further in view of Tzipori should therefore be withdrawn.

Objective Indicia of Nonobviousness

Further, even if the combination of Speirs or O'Brien with Carter or Shitara and with Tzipori did establish a *prima facie* case of obviousness, which it does not, objective indicia can be used to overcome the rejection of claims 1, 2, 14, 17-20, 23, 29, and 32-55 under 35 U.S.C. § 103(a) for obviousness. The M.P.E.P. § 716.01(a) states:

Affidavits or declarations, when timely presented, containing evidence of criticality or unexpected results, commercial success, long-felt but unsolved needs, failure of others, skepticism of experts, etc., must be considered by the examiner in determining the issue of obviousness of claims for patentability under 35 U.S.C. 103. The Court of Appeals for the Federal Circuit stated in *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538, 218 USPQ 871, 879 (Fed. Cir. 1983) that "evidence rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness." Such evidence might give light to circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or unobviousness, such evidence may have relevancy. *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966); *In re Palmer*, 451 F.2d 1100, 172 USPQ 126 (CCPA 1971); *In re Fielder*, 471 F.2d 640, 176 USPQ 300 (CCPA 1973).

M.P.E.P. § 716.04 sets forth the three criteria for establishing a long felt need as follows:

1: The need must have been a persistent one that was recognized by those of ordinary skill in the art.

2: The long-felt need must not have been satisfied by another before the invention by applicant.

3: Third, the invention must in fact satisfy the long-felt need.

Applicants' specification teaches that there is a need for an agent that treats or prevents Shiga-toxin associated diseases including hemolytic uremic syndrome (HUS). HUS is characterized by acute renal failure, hemolytic anemia, fever, and thrombocytopenia, and is one of the most common causes of acute renal failure in children. Applicants also state that "currently there is no known cure or vaccine for ... HUS" and point out that "there is a need in the art to provide monoclonal antibodies that can bind to Shiga toxins which could prevent or lessen the devastating effects of these toxins." These facts, outlined in the specification, demonstrate that the need for an agent that treats or prevents Shiga-toxin associated diseases was a persistent one recognized by those in the art (criteria 1, above) and that this need has not been met by others (criteria 2, above).

Applicants' have designed antibodies that solve a problem scientists have been

tackling for years. Indeed practitioners in the field immediately recognized that Applicants' antibodies represented a remarkable potential advance in treating HUS. As evidence of this assertion, Applicants direct the Examiner's attention to a letter (copy attached as Exhibit B) from the U.S. Food and Drug Administration (FDA) to Caprion Pharmaceuticals, the exclusive licensee of the present application. The FDA states that a clinical development program designed to utilize Applicants' claimed monoclonal antibodies to Shiga toxin has been granted "fast-track designation" for the treatment of Shiga toxin-producing bacterial infections. In granting fast-track designation, the FDA stated:

[HUS] is a serious condition that may result from infection with Shiga toxin-producing bacteria. There are currently no therapies available for the prevention of this condition in infected patients. Chimeric monoclonal antibodies to Shiga toxins 1 and 2 have the theoretical potential to address this unmet medical need.

Clearly the FDA notes that there is an "unmet medical need" for treating infections resulting from Shiga toxin producing bacteria (criteria 1 and 2, above.) Moreover, the FDA makes clear that Applicants' antibodies address this unmet need (criteria 3, above.) The FDA's recognition that Applicants' antibodies deal with an unmet medical need, and that these antibodies represent a remarkable advance in the field, is indicative of invention. Applicants have satisfied all three of the criteria set forth in MPEP § 716.04 for establishing a long felt need and submit that these objective indicia should be

considered by the Examiner as a further basis for overcoming the obviousness rejection. For this reason as well, Applicants respectfully request that the rejection of claims 1, 2, 14, 17-20, 23, 29, and 32-55 under § 103 for obviousness be withdrawn.

Rejections under the Judicially Created Doctrine of Obviousness-Type Double Patenting

Claim 41 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 9 of U.S. Patent No. 5,747,272. Claim 41 has been cancelled by the present amendment. This rejection is now moot.

Claims 1-2, 14, 17-20, 23, 29, and 32-43 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 9 of U.S. Patent No. 5,747,272 in view of Carter et al. (WO 94/04679; “Carter”). For the reasons discussed above in connection with the obviousness rejection, the Office has failed to establish that one skilled in the art, in view of the ‘272 patent, would be motivated to modify the teachings of claim 9 to arrive at the presently claimed invention. In addition, Applicants present strong evidence of the nonobviousness of the presently claimed invention. The nonstatutory obviousness-type double patenting rejection over claim 9 of the ‘272 patent in view of Carter should be withdrawn.

CONCLUSION

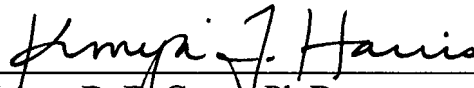
Applicants submit that the pending claims are in condition for allowance and such action is respectfully requested.

Enclosed is a Petition to extend the period for filing a reply for three months to and including May 30, 2007.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: may 30, 2007

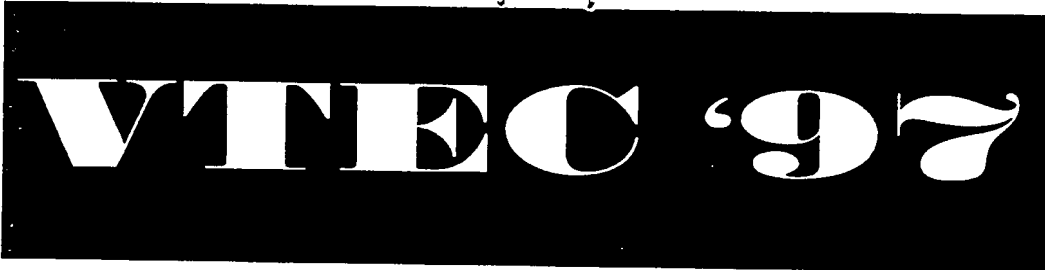


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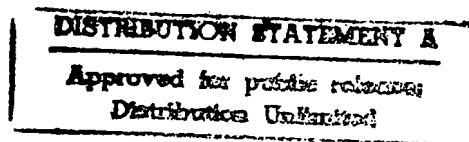
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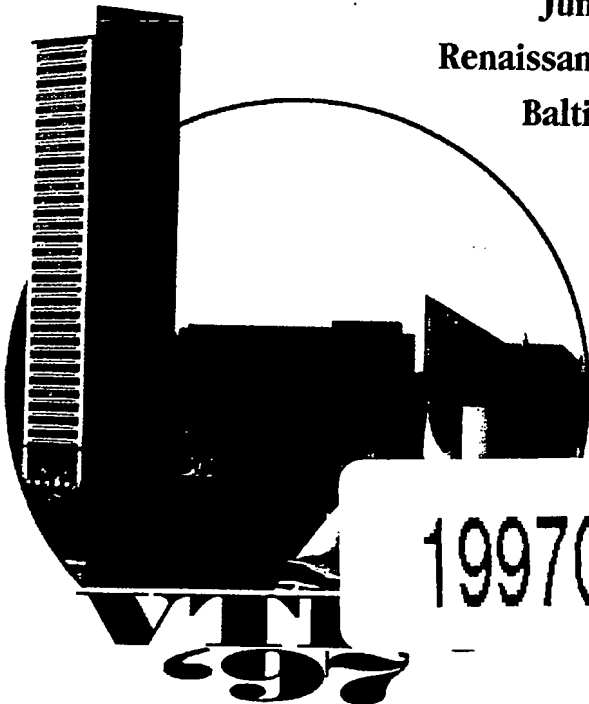
Exhibit A



3rd International Symposium
and Workshop on
Shiga Toxin (Verocytotoxin) – Producing *Escherichia Coli* Infections



June 22–26, 1997
Renaissance Harborplace Hotel
Baltimore, Maryland
USA



19970818 017



under the auspices of the Lois Joy Galler Foundation for Hemolytic Uremic Syndrome, Inc.

AD _____

GRANT NUMBER DAMD17-96-1-6308

TITLE: Third International Symposium of Shiga Toxin
(Verocytotoxin) - Producing Escherichia Coli Infections
(VTEC '97)

PRINCIPAL INVESTIGATOR: Alison O'Brien

CONTRACTING ORGANIZATION: Lois Joy Galler Foundation
Hemolytic Uremic Syndrome, Inc
Melville, New York 11747

REPORT DATE: October 1997

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Wednesday, June 25

SESSION VII

TREATMENT OF DISEASE DUE TO STEC (Chair: Bernard Kaplan)

- 2:10–2:35 *Marguerite A. Neill*
Infectious disease management
- 2:35–3:00 *Kevin Meyers*
Treatment of HUS and other complications
- 3:00–3:30 COFFEE
- 3:30–4:10 *Glen D. Armstrong and Peter Rowe*
Clinical trials of Synsorb Pk in preventing HUS

UBMITTED TALKS

- 4:10–4:25 *A. Edwards, K. Arbuthnott, J.R. Stinson, H.C. Wong, C. Schmitt, and A. O'Brien*
Humanization of monoclonal antibodies against *Escherichia coli* toxins Stx1 and Stx2
- 4:25–4:40 *T. Takeda, M. Tanimura, K. Yoshino, E. Matsuda, H. Uchida, and N. Ikeda*
Early use of antibiotics for STEC O157 infection reduces the risk of hemolytic uremic syndrome
- 4:40–4:55 *A.I. Stewart, G.A. Jones, J. McMenamin, A.K.R. Chaudhuri, and W.T.A. Todd*
Central Scotland *Escherichia coli* O157 outbreak (Clinical Aspects)
- 4:55–5:45 Roundtable discussion
Bernard Kaplan
Marguerite A. Neill
Gianfranco Rizzoni
Mark Taylor
Richard Siegler
Phillip Tarr

HUMANIZATION OF MONOCLONAL ANTIBODIES
AGAINST *ESCHERICHIA COLI* TOXINS STX1 AND STX2

V110/VII

Ana Edwards, Kathy Arbuthnott, Jeffrey R. Stinson*, Hing C. Wong,
Clare Schmitt, and Alison O'Brien
Sunol Molecular Corporation, Miami, Florida and the Department of
Microbiology, USUHS, Bethesda, Maryland

The murine monoclonal antibodies 13C4 and 11E10 are specific for the Shiga toxins types 1 and 2, respectively, that are expressed by Enterohemorrhagic *E. coli*. These antibodies are capable of neutralizing the toxins both in tissue culture and animal models. For the purpose of developing therapeutic agents to treat or prevent hemolytic uremic syndrome, we have humanized these monoclonals. Total RNA from the hybridoma cell lines and mouse antibody variable region primer sets were used for RT-PCR to amplify the variable regions. The V regions were then cloned into a mammalian expression vector for the production of mouse variable region:human IgG1/kappa chimeric antibodies. NS0 cells were transfected with the vector and the humanized antibodies produced recognize the toxins in an enzyme immunoassay. The protective capacity of these antibodies in an animal model system is being tested and the results will be discussed.

THE RESISTIVE INDEX IN D+ AND D- HUS: IS THERE A
CLINICAL CORRELATION?

V111/VII

Seth L. Schulman*, Peter Feola, Kevin E. C. Meyers, Richard D. Bellah and Bernard S. Kaplan. Divisions of Pediatric Nephrology and Radiology, The Children's Hospital of Philadelphia and University of Pennsylvania School of Medicine, Philadelphia, PA. USA

Several reports have documented the utility of the resistive index (RI) obtained with Doppler sonography in the acute phase of HUS as clinically significant and a potential guide to therapy. We analyzed our experience with RI in children with both D+ and D- HUS with a view toward predicting the need for therapy and prognosis. Sixteen children with HUS had renal Doppler ultrasonography early in the course of their illness. Eleven children, mean age 7.0 y had D+ HUS, the remaining 5, mean age 0.9 y had D- HUS [Denys-Drash (2), meningococcemia, *S. pneumoniae* and idiopathic]. RIs were determined blindly without knowledge of the type of HUS and read as normal or elevated for age. Abnormal RIs were observed in 6/11 children with D+ HUS. Anuria was present in only 3/6 cases, all have normal renal function on follow-up. Of the 5 with normal RIs, 3 had anuria, 1 has decreased renal function. All 5 patients with D- HUS had normal RIs; 4 required dialysis, 2 have normal renal function. We conclude that the RI offers no value in determining the need for dialysis and should not be performed routinely. Patients with D- HUS who would be expected to have increased renovascular resistance by the nature of their pathology did not demonstrate this abnormality on Doppler sonography.

Exhibit B



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 12926

Caprion Pharmaceuticals, Inc.
Attention: Mariam Mehran, PhD
Director, Clinical Development
7150, Alexander-Fleming
Montreal, Quebec, Canada, H4S-2C8

Dear Dr. Mehran:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the Act) for Chimeric Monoclonal Antibodies to Shiga Toxins 1 and 2 for the Treatment of Shiga Toxin Producing Bacterial Infection.

We also refer to your March 6, 2006, request for fast track designation submitted under section 506 of the Act.

We have reviewed your request and have concluded that it meets the criteria for fast track designation. Therefore, we are designating Chimeric Monoclonal Antibodies to Shiga Toxins 1 and 2 for the Treatment of Shiga Toxin Producing Bacterial Infection as a fast track product.

We are granting fast track designation for the following reasons:

Hemolytic-uremic syndrome is a serious condition that may result from infection with Shiga-toxin-producing bacteria. There are currently no therapies available for the prevention of this condition in infected patients. Chimeric monoclonal antibodies to Shiga toxins 1 and 2 have the theoretical potential to address this unmet medical need.

If you pursue a clinical development program that does not support use of Chimeric Monoclonal Antibodies to Shiga Toxins 1 and 2 for the Treatment of Shiga Toxin Producing Bacterial Infection, we will not review the application under the fast track development program.

IND 12926

Page 2

If you have any questions, call Carmen DeBellas, Regulatory Project Manager, at (301)796-1203.

Sincerely,

[See appended electronic signature page]

Janice M. Soreth, MD

Director

Division of Anti-Infective and Ophthalmology Products

Office of Antimicrobial Products

Center for Drug Evaluation and Research

Linked Applications

Sponsor Name

Drug Name

IND 12926

CAPRION PHARMS

Chimeric Monoclonal Antibodies caStx1
and caStx2

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/s/

FRANCES LESANE

05/05/2006

JOHN J ALEXANDER

05/05/2006